REMARKS

The Office Action mailed July 10, 2003 has been received and reviewed. Claims 7 through 11, 14, and 17 through 19 are identified as pending in the Office Action. Claims 14, 17 and 18 have been canceled without prejudice or disclaimer and applicants reserve the right to pursue the subject matter of these claims in one or more related applications. Applicants have amended claims 7, 8, 9, 10, 11 and 19 and added new claims 20 and 21. Reconsideration of the application as amended is respectfully requested.

Applicants note that the objection to claim 9, the rejection of claims 7, 8, 14, 17 and 18 under 35 U.S.C. § 102(b), the rejection of claims 7 and 14 under the first paragraph of 35 U.S.C. § 112 and the rejection of claim 7 and 14 under the second paragraph of 35 U.S.C. § 112 have been withdrawn. The attention of the Examiner to the application, and the withdrawal of each and every objection and rejection in the prior Office Action are noted with appreciation. The newly presented rejections are addressed below.

35 U.S.C. § 112, First Paragraph, Rejections

Claims 7-1, 14 and 17-19 were rejected in the Office Action as assertedly lacking enablement under 35 U.S.C. §112, first paragraph. Claims 14, 17 and 18 have been canceled rendering this rejection moot as to them. With respect to the remaining claims, applicants respectfully submit that, as amended, independent claims 7 and 19 are enabled, as are the claims dependent therefrom.

The Office Action states that the specification while "enabling for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of a *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutical acceptable carrier, wherein the mutated bacterium lacking flagellin does not reasonably provide enablement for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of any *Salmonella* mutated bacterium wherein the mutated bacterium lacking flagellin and wherein the mutated bacterium is attenuated." (Office Action at page 3, underlining in original).

The Office Action states the "specification has shown that the vaccines comprising mutated bacterium lacking flagellin from *S. typhimurium* STMP are protective. It is determine[d] that there

are limited working examples commensurate in scope with the instant claims and that these is limited guidance provided in the specification as to how to make and use vaccine compositions that comprise a mutated from any *Salmonella* bacterium (other than STM2000) lacking flagellin that are protective against Salmonellosis" (Office Action at page 11, underlining in original). As noted in the Office Action at pages 4-5, Example 3 of the specification demonstrates that two different vaccines strains, comprising STMP and STM2000, were able to reduce fecal shedding of a challenge strain significantly and that STMP and STM2000 inoculated chickens survived compared to an 80% death rate for those inoculated with a wildtype vaccine.

In addition to Example 3, Example 2 at page 18 of the present application discloses vaccines comprising flagellated and non-flagellated *Salmonellas,* specifically *S. entireditis* fla^+ and *S. entireditis* fla^-. The results of Example 2 show that *S. entireditis* fla^- vaccines provide a clearly recognizable marker. The present specification thus teaches effective marker vaccines using *Salmonella* bacteria lacking flagellin, other than STM2000, and provides support for additional strains at page 6, lines 4-15 and page 9, lines 10-12.

Claims 7 and 19 are directed to a marker vaccine that allows exposure of an animal to a wild-type strain to be detected by antibody testing. The present specification thus discloses and enables manufacture and use of such vaccines with multiple *Salmonella* strains. Accordingly, it is respectfully submitted that claims 7 and 19, as amended, are fully enabled.

Further, the Office Action examines three references, Lockman et al., *Infection and Immunity*, Jan. 1990, p. 137-143 (hereinafter "Lockman"), Wahden et al., *Bull. World Health Organization*, vol. 52, 1975 (hereinafter "Wahdan"), and Hackett et al., *J. Infectious Diseases*, vol. 157, January 1988 (hereinafter "Hackett"). At pages 5 to 10, the Office Action examines each of these references with respect to the characterization of flagella as virulence factors to state that the "role of attenuation to produce *Salmonella* nonflagelated mutants is unclear." (Office Action at page 10, underlining in original). From this examination, it is concluded that the "skilled artisan is forced into undue experimentation to practice (make and use) the invention as it is broadly claimed because the prior [art] has taught that many strains of fla^- are not protective, do not confer protection from

subsequent challenge by motile *Salmonella* bacteria and that mutations such as the flaF25 in the attenuation of Salmonella bacterium is unclear." (Office Action at page 11, underlining in original).

With respect to Wahdan, applicants respectfully point out that the reference relates to *S. typhi* and *S. paratyphi A / B*, which are not claimed in the instant claims. Second, as acknowledged by Wahdan (p. 72, right column, last lines) "It seems more probable that a property other than the synthesis of the flagellar antigen determines immunogenicity and is absent from this non-motile motif." In view of Wahdan, applicants respectfully submit that non-flagellin-related components of the non-mobile mutant lead to the lack of immunogenicity.

With respect to Hackett, Hackett used only FlaF25-strains for the experiments.

Lockman, the other reference cited in the Office Action, discusses at page 137, right column, the paper by Hackett, saying "Recently, Carsiotis et al. reported that the mutation involved not only some of the genes encoding the biosynthesis of flagella but extended into previously undescribed virulence genes. Thus the role of the flaF25 mutation in the attenuation of *S. typhimurium* in mice remained unclear", *i.e.*, the effects seen by Hackett cannot be attributed to the presence or absence of flagella; they relate to the deletion of the previously undescribed virulence factors.

Besides questioning the work of Hackett, Lockman concludes, as have the applicants, that "wild-type SR-11 and the isogenic nonflagellated and non-motile mutants were equally virulent in mice challenged via intraperitoneal injection." Lockman shows that non-immunogenic fla^{minus}-mutants are incapable of inducing immunity due to deletion of virulence genes, not due merely to the fact that they are fla^{minus}.

Applicants have shown (*e.g.*, in Example 2), that *S. enteritidis* fla^{minus} bacteria provide a clearly recognizable marker. In contrast to Hackett, Examples 3 and 4 show that live attenuated flagella-less *S. typhimurium* vaccine according to the invention give excellent results in both chickens and pigs (Hackett also tried to use *S. typhimurium.*) Lockman is correct that rendering a live attenuated $fla^{positive}$ strain into a fla^{minus} strain does not change the virulence of the strain. Hackett is simply wrong on the point. With this knowledge, no reason can be seen to assume that applicants' successful approach will not be successful with the claimed Salmonella strains, and the claims should be considered fully enabled.

The specification states, at page 10, beginning at line 13, that:

> **Surprisingly, vaccines according to the invention do not show significant differences in virulence when compared to their flagella-bearing counterparts**. In other words, removal of the flagellin gene does not significantly change the level of attenuation. This has the unexpected advantage that both future and approved existing live attenuated *Salmonella* strains suitable for use in vaccines can be used in the present invention as soon as they are made non-capable to induce antibodies against at least one antigenic determinant of flagellin or flagella.

As acknowledged in the Office Action, the presence or absence of flagella has little influence on the virulence. In view of this fact, the present invention makes it possible to take existing live attenuated vaccine strains (*i.e.*, those of the claimed *Salmonella* species) and make a marker vaccine from them without essentially changing the virulence of the vaccine strain. The specification demonstrates at Examples 3 and 4, that fla$^-$ vaccines exhibit this protective function in both chickens and pigs. In connection with Example 2, these further demonstrate that fla$^-$ vaccines manufactured from different strains are capable of serving as marker vaccines. As discussed previously herein, each of independent claims 7 and 19, as amended, is directed to a marker vaccine. A marker vaccine allows a subsequent exposure of an animal to a wild-type strain to be detected by antibody testing. The present specification thus clearly enables manufacture and use of such vaccines with multiple *Salmonella* strains. Accordingly, applicants respectfully submit that independent claim 7, with claims 8-11 dependent therefrom, and independent claim 19 are enabled. It is requested these claims be allowed.

New Claims

At page 3, the Office Action states the specification is "enabling for a vaccine composition for the protection against Salmonellosis comprising an immunologically effective amount of a *Salmonella typhimurium* STMP mutated bacterium and a pharmaceutical acceptable carrier, wherein the mutated bacterium lacking flagellin...." New claims 20 and 21 are directed to this disclosure

noted as enabled in the Office Action. Accordingly, it is requested that new claims 20 and 21 be allowed.

CONCLUSION

All pending claims are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Examiner is respectfully invited to contact applicants' attorney.

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